

# **A Biological Approach for the Treatment of Prostate Cancer**

***pPSA +/- pIL-18***

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*Deborah Marshall, Ph.D.*

# Rationale for treating prostate cancer with specific-active immunotherapy

- ◆ Prostate cancer patients do not have any effective treatments once they fail anti-androgen therapy (large unmet need)
- ◆ PSA (prostate specific antigen) is a tissue-specific tumor associated antigen, and is secreted by normal and transformed prostate epithelial cells
- ◆ PSA-specific immune responses are detected in some prostate cancer patients, suggesting tolerance may be broken
- ◆ An anti-PSA immune response would only destroy the prostate and the tumor; no other tissues should be affected



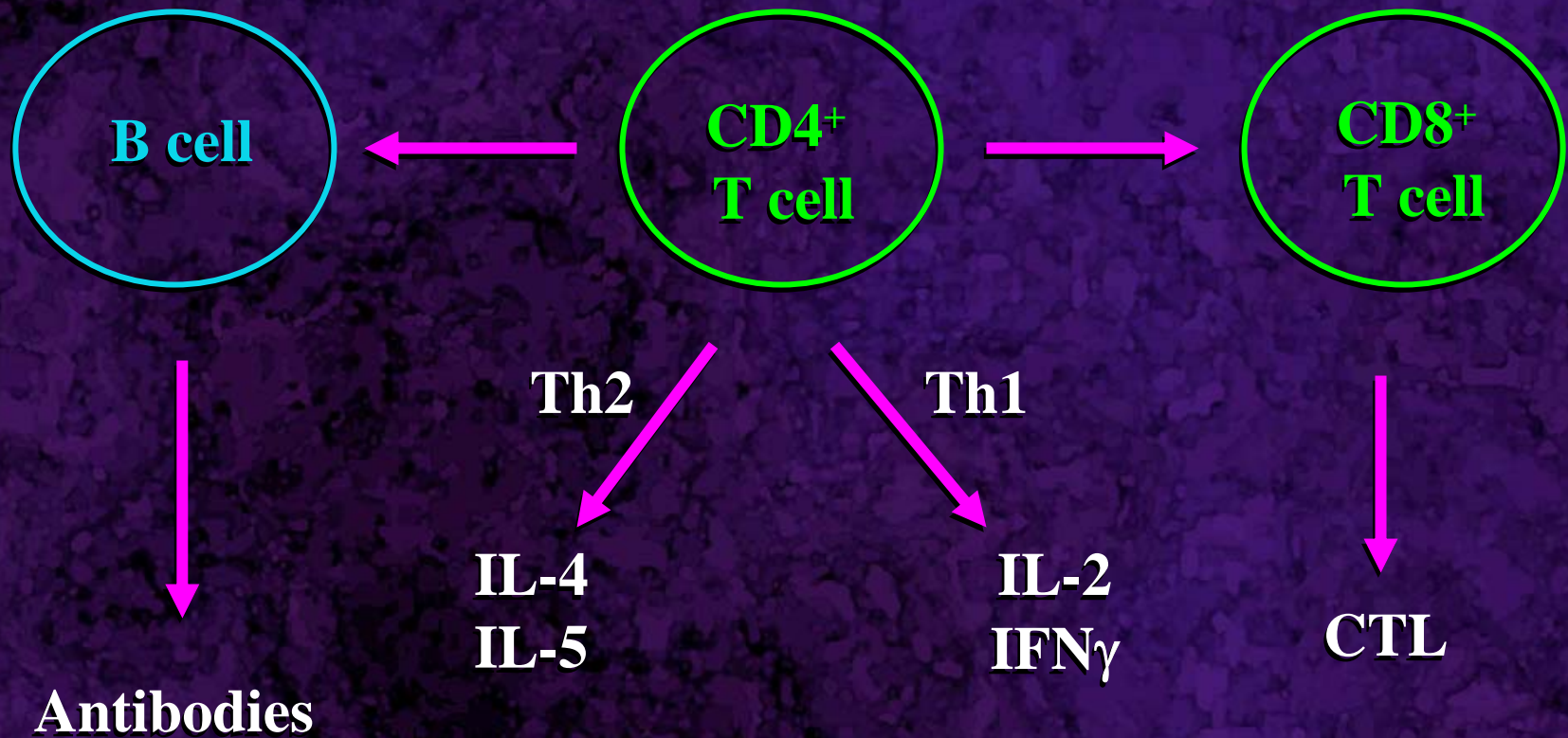
# Hypothesis

A DNA vaccine encoding PSA will generate a therapeutic cellular immune response against PSA-expressing tumor cells.

Skewing this response toward Th1 by co-injecting an IL-18 DNA adjuvant plasmid will enhance this immune response.

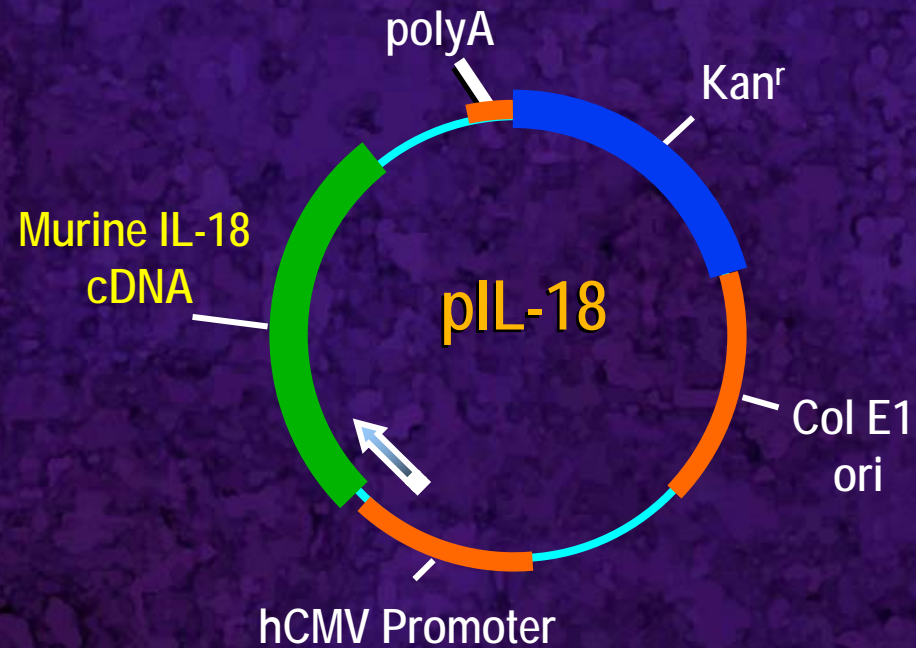
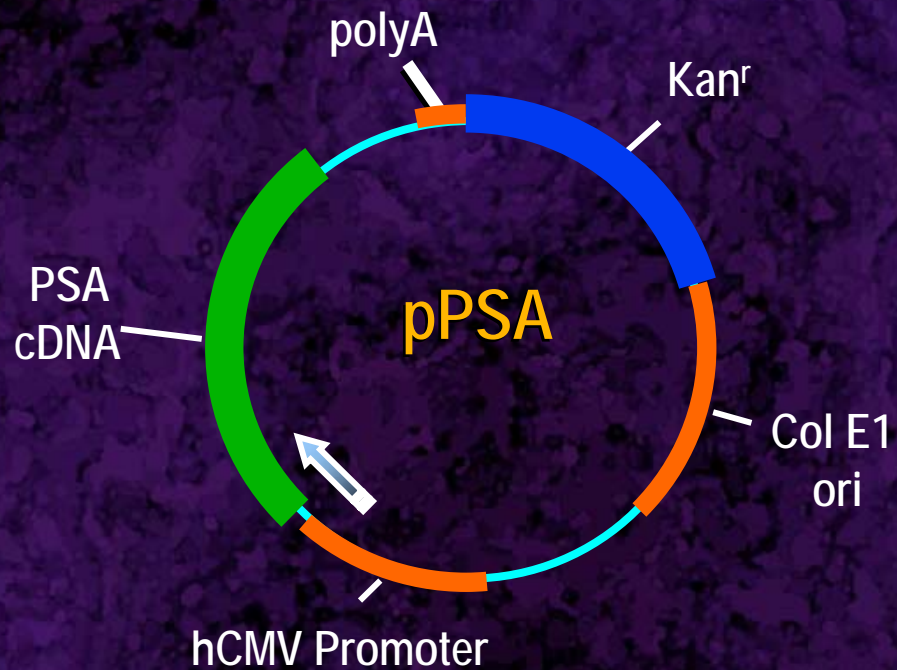


# The breadth of the immune response is important





# DNA Vaccines





# Tumor model for evaluation of pPSA/pIL-18 DNA vaccine

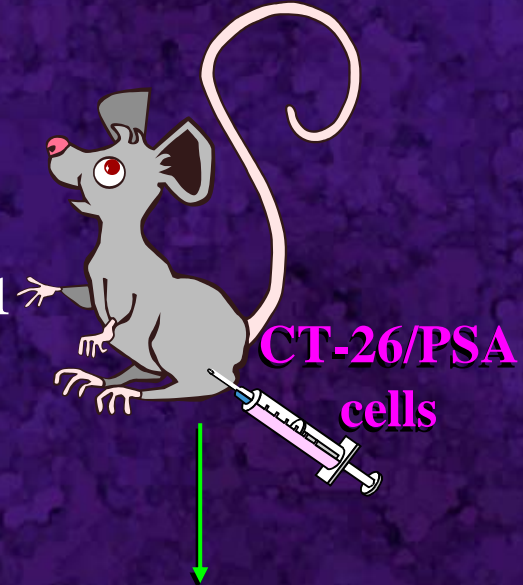


pPSA -/+  
pIL-18

Inject DNA at  
Days 0, 14

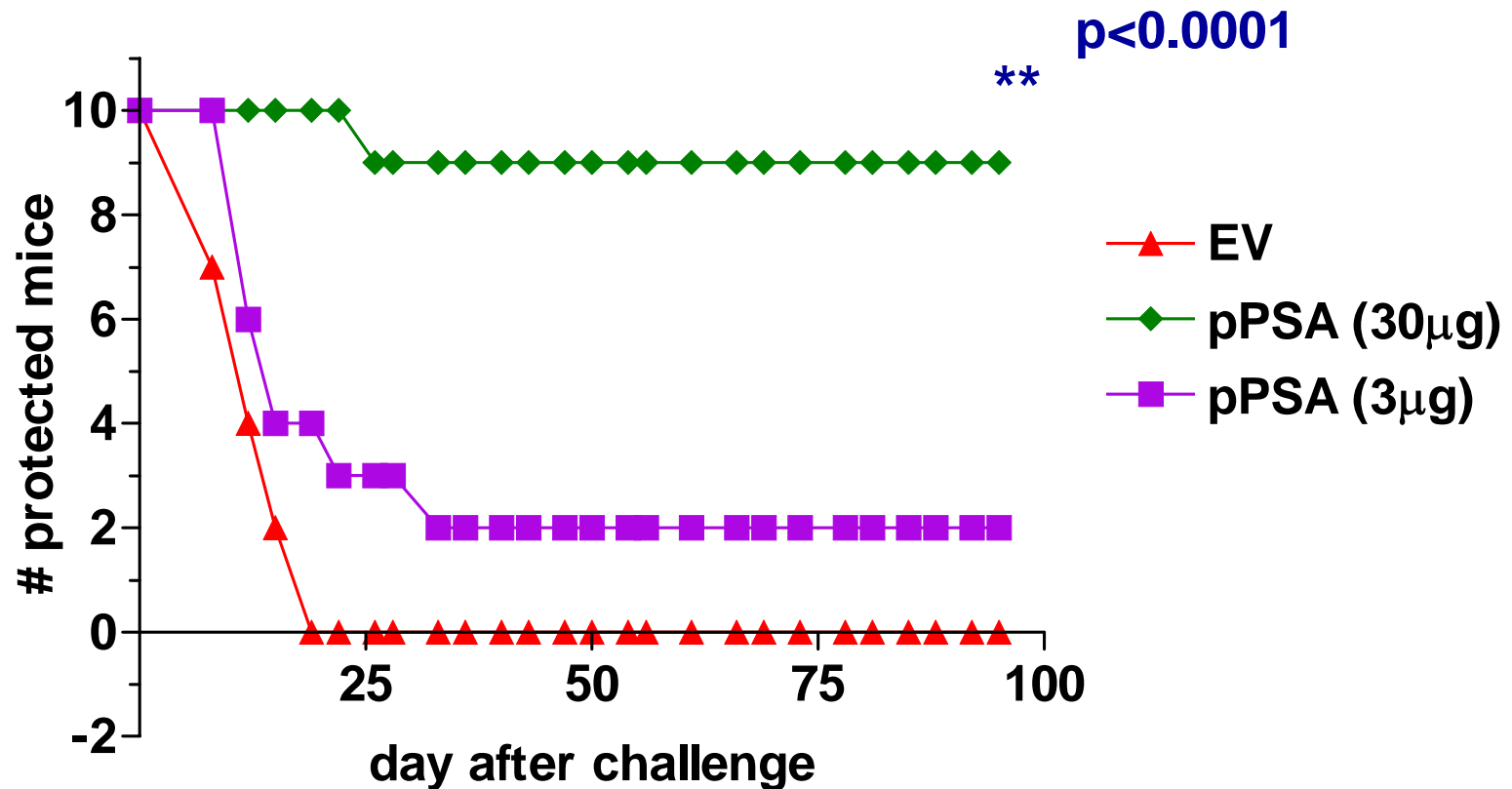


Inject tumor  
cells on day 21



Monitor for  
tumor growth

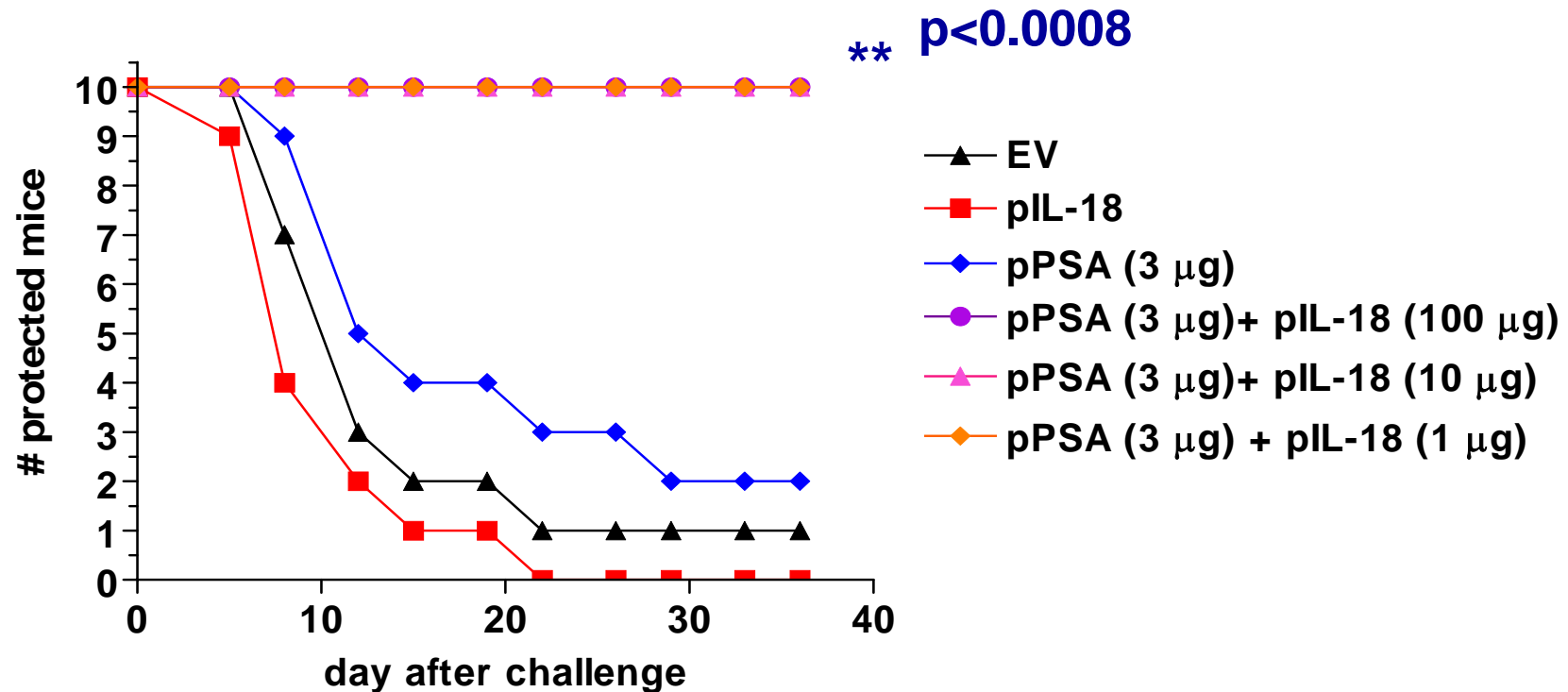
# pPSA DNA vaccine protects against tumor development



Long term immune memory response induced



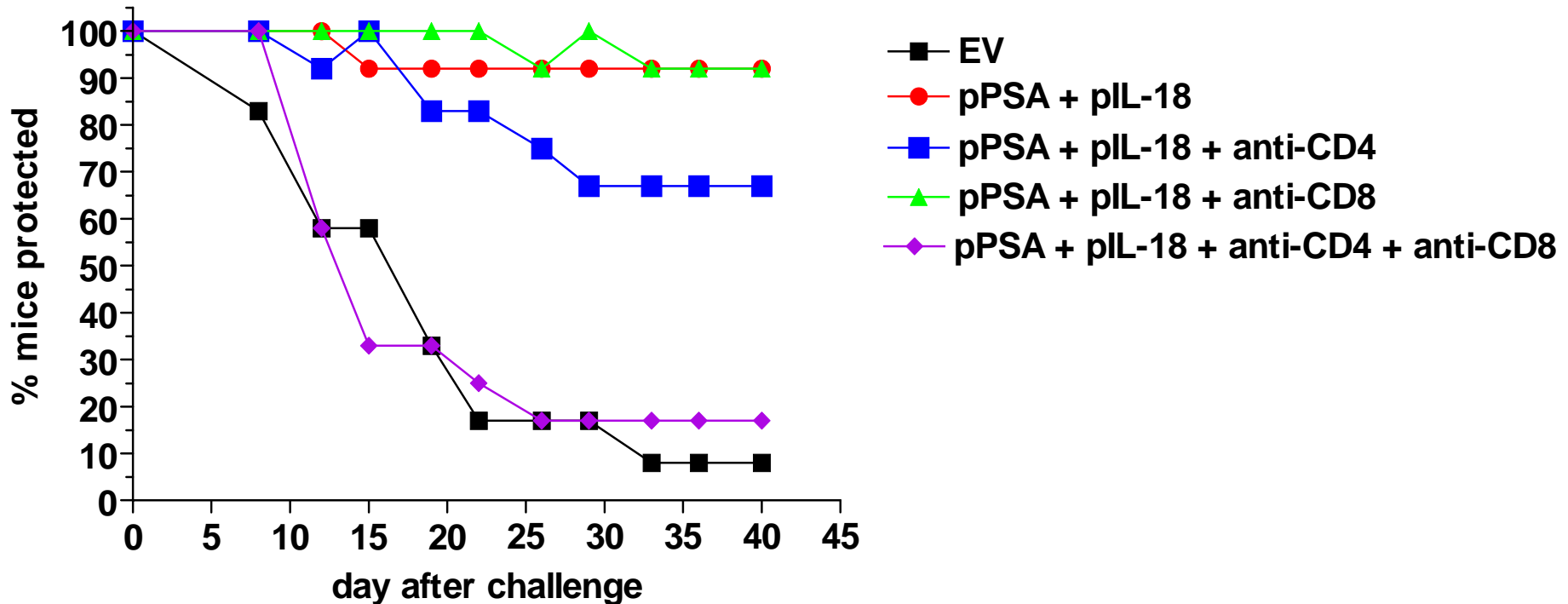
# pIL-18 enhances tumor protection in pPSA-immunized mice




100% tumor protection observed when sub-optimal doses of pPSA are co-administered with pIL-18



# Both CD4 and CD8 T cells are required for PSA-specific anti-tumor immunity



# Experimental design for immune response assessments


  
pPSA -/+  
pIL-18

Inject DNA  
at days 0, 14,  
28 and 42



Isolate splenocytes

Isolate sera

  
↓  
Proliferation assay  
Bioplex assay  
CTL assay

  
↓  
Ab



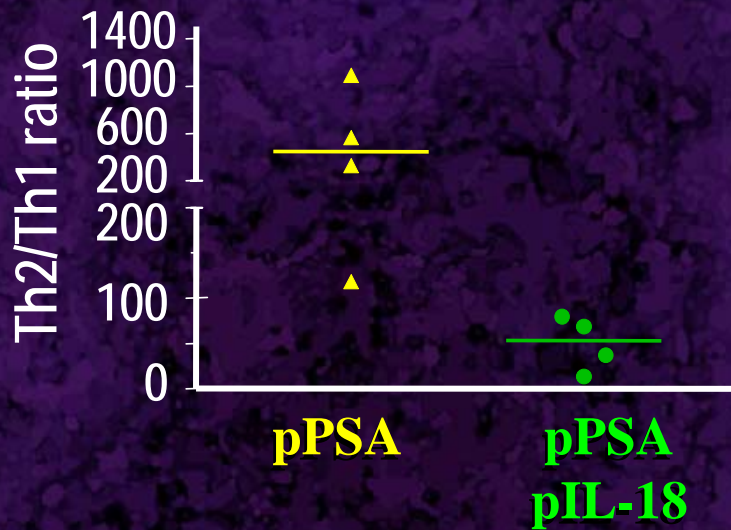
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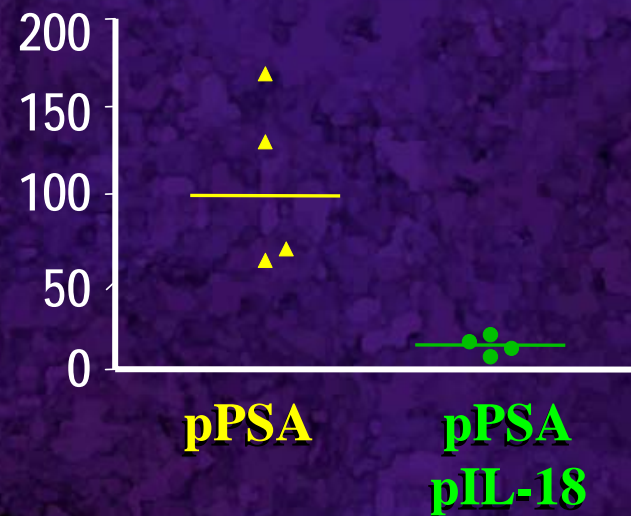


# pIL-18 enhances Th1 skewing of antibody responses to PSA

Th2/Th1 ratios after one immunization



Th2/Th1 ratios after four immunizations

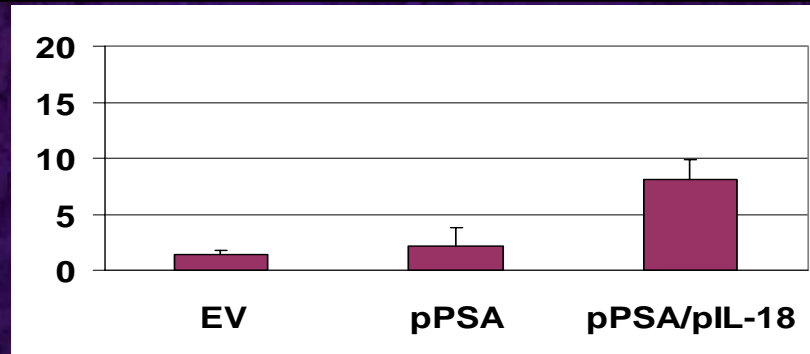


Th2 = IgG1  
Th1 = IgG2a

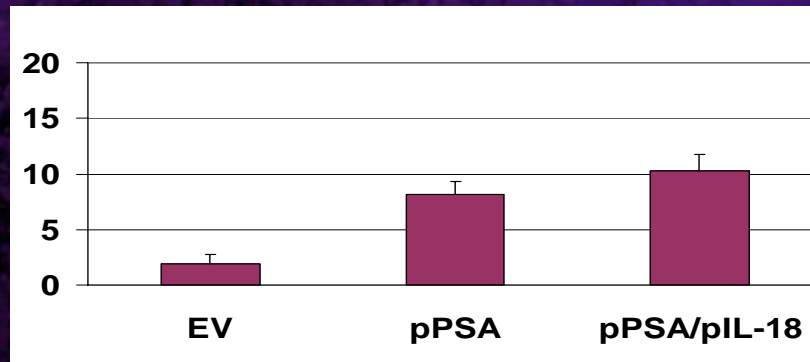


# pIL-18 immunization enhances early cellular proliferative responses

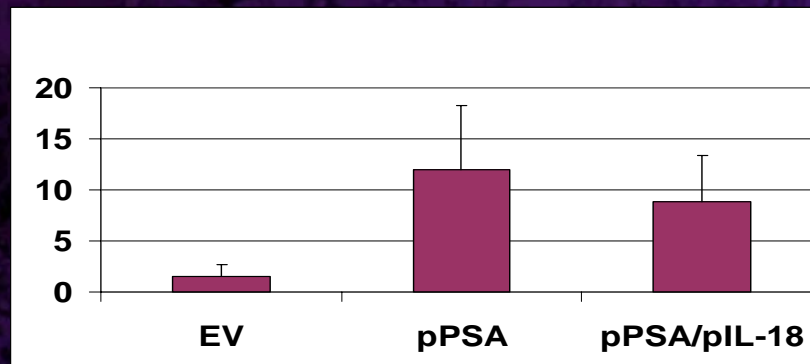
1 inoculation



2 inoculations



3 inoculations

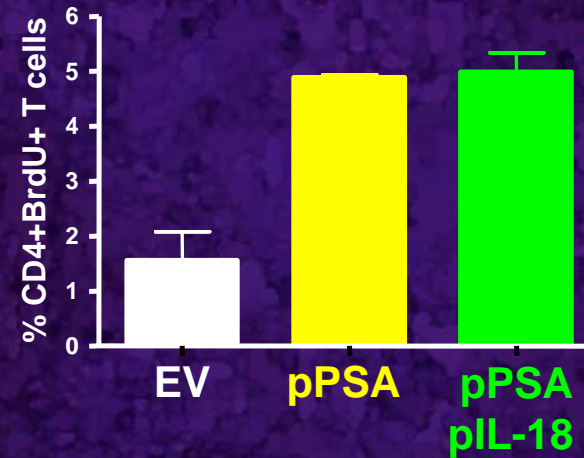
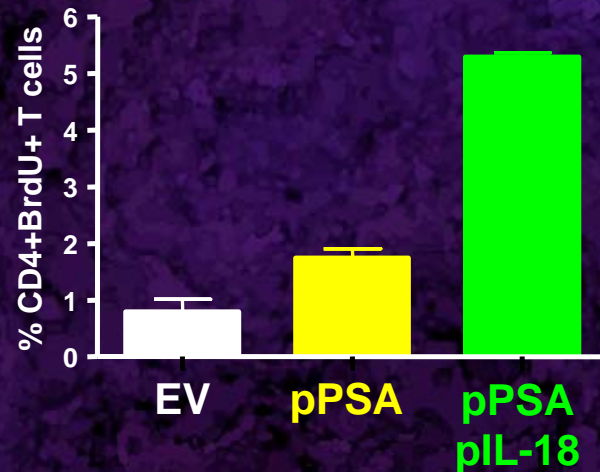


# pIL-18 enhances the kinetics of the CD4<sup>+</sup> and CD8<sup>+</sup> T cell response

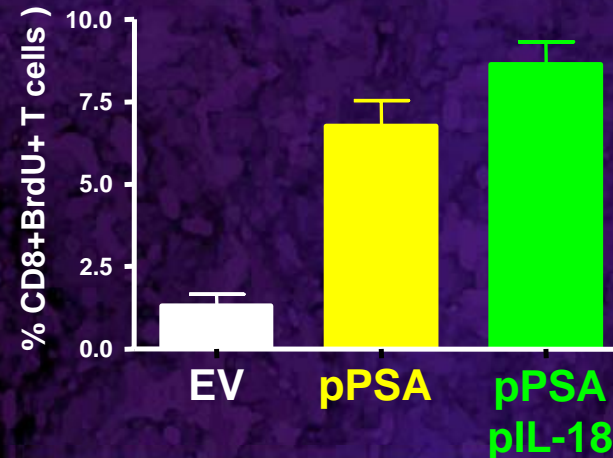
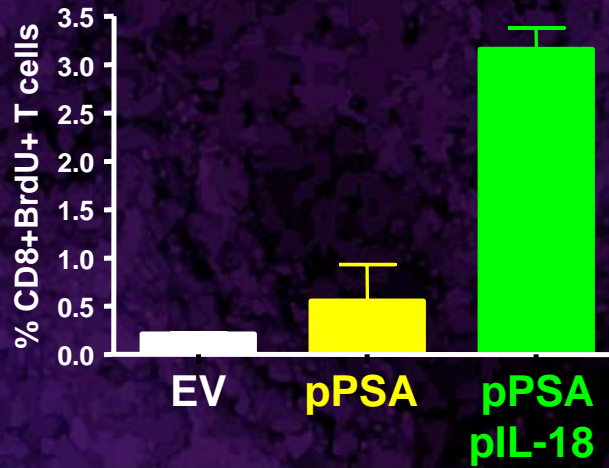
1 inoculation

2 inoculations

CD4



CD8

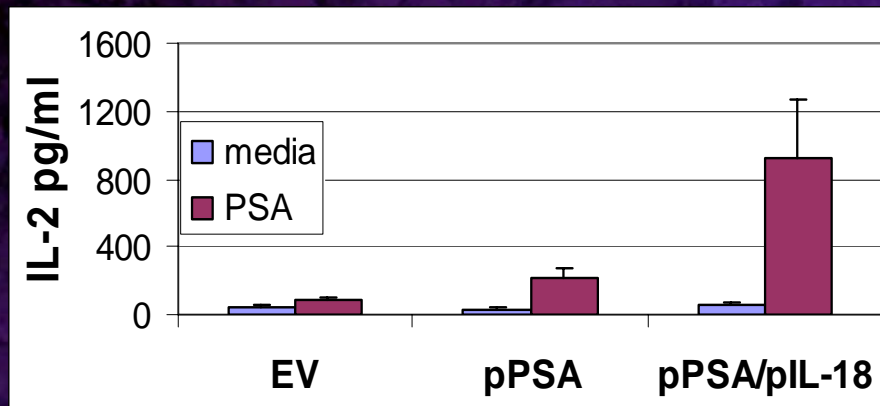




# pPSA + pIL-18 elicits a stronger Th1 response than pPSA alone

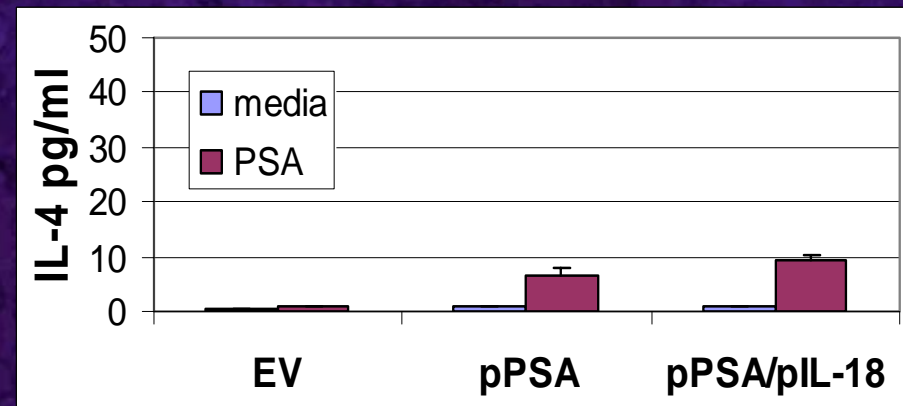
IL-2

Th1

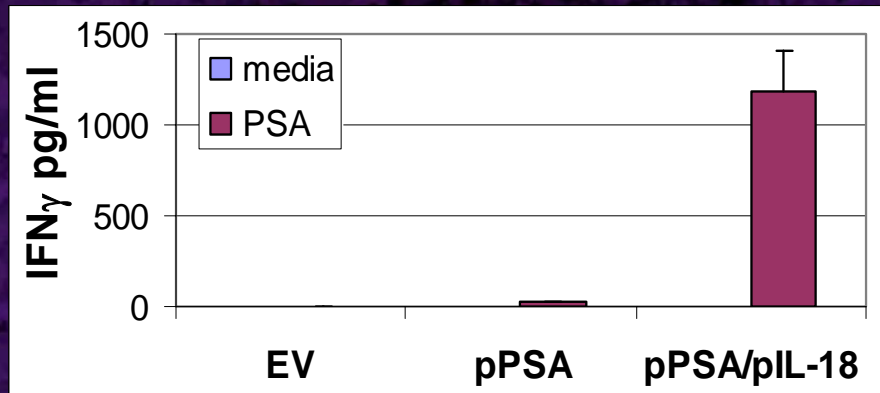


IL-4

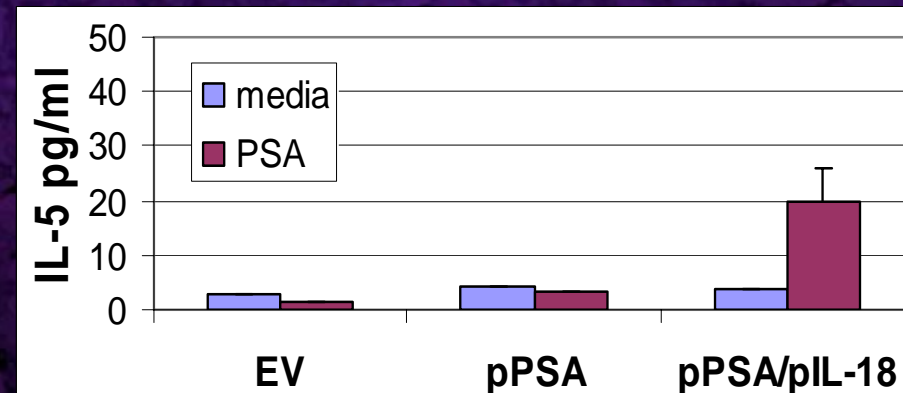
Th2



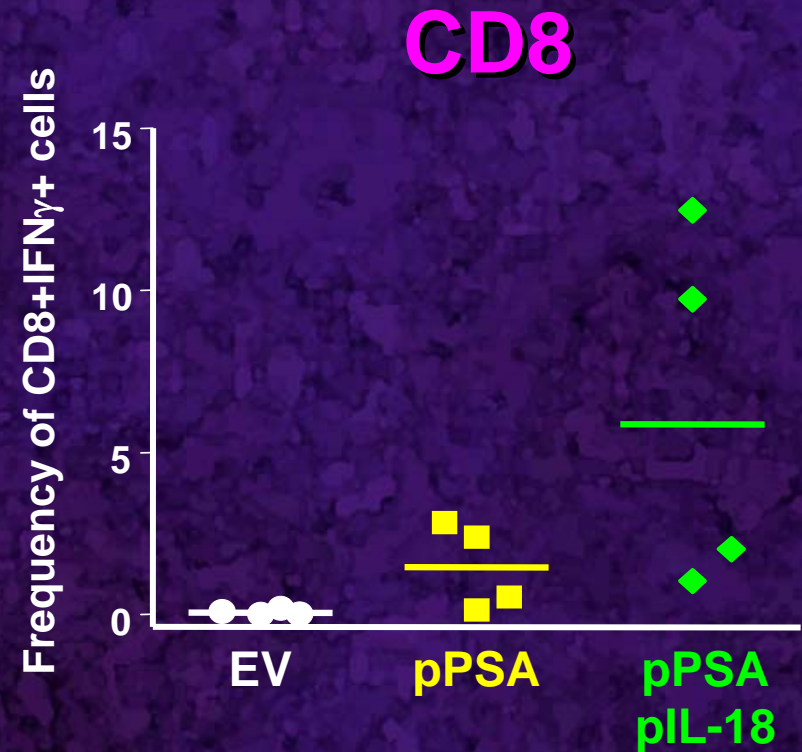
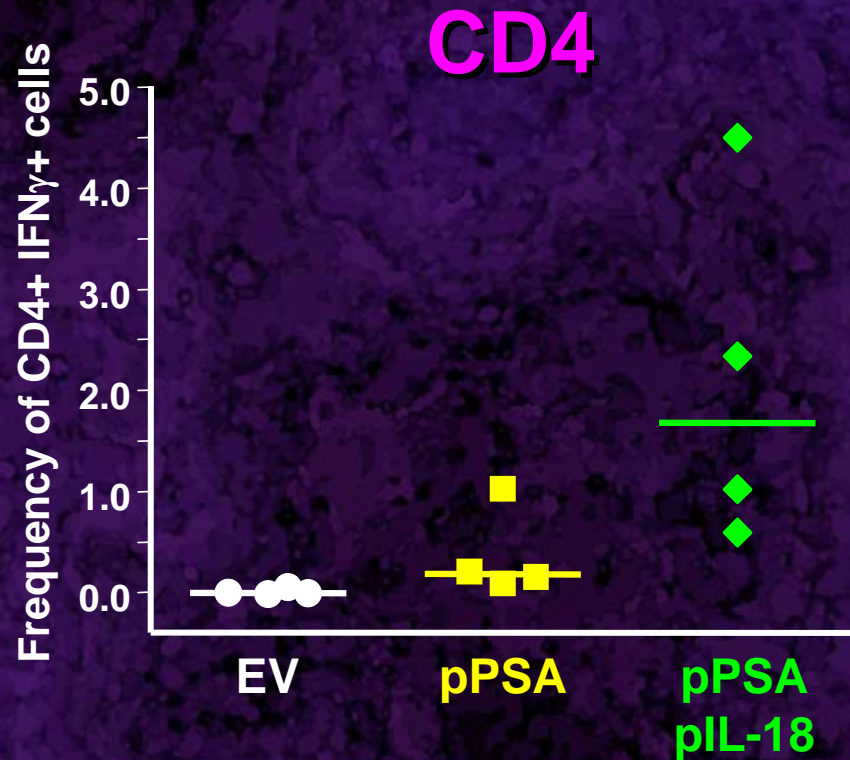
IFN $\gamma$



IL-5



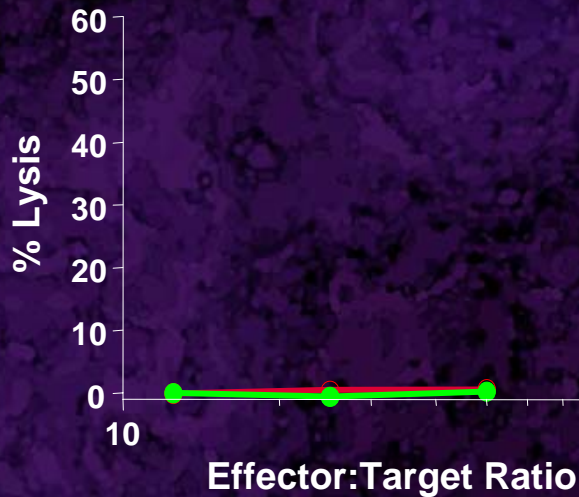
# pIL-18 enhances the frequency of IFN $\gamma$ + CD4<sup>+</sup> and CD8<sup>+</sup> T cells



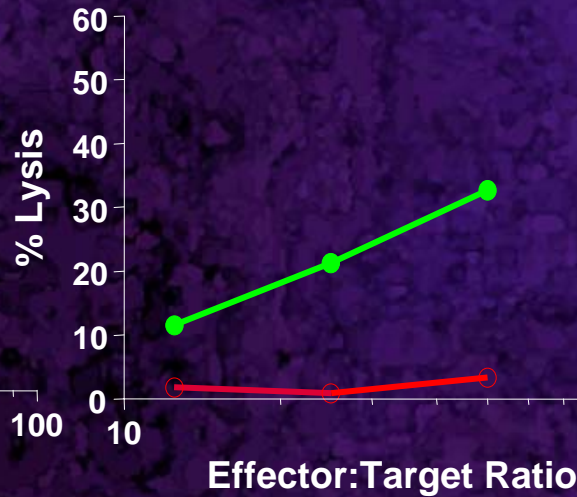


# pPSA +/- pIL-18 enhances PSA-specific CTL responses

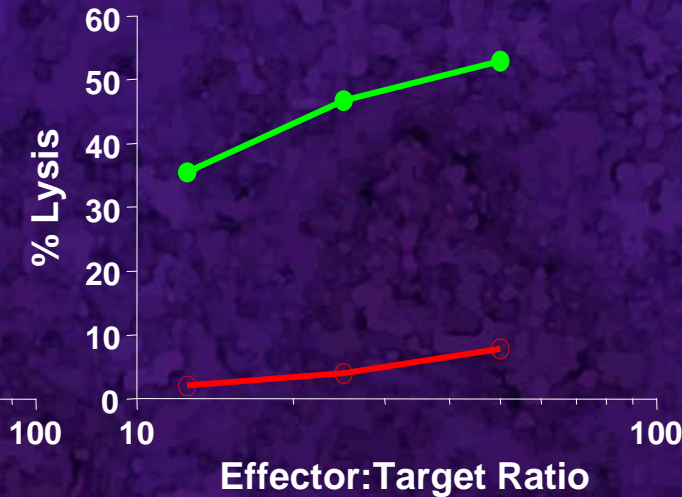
EV



pPSA

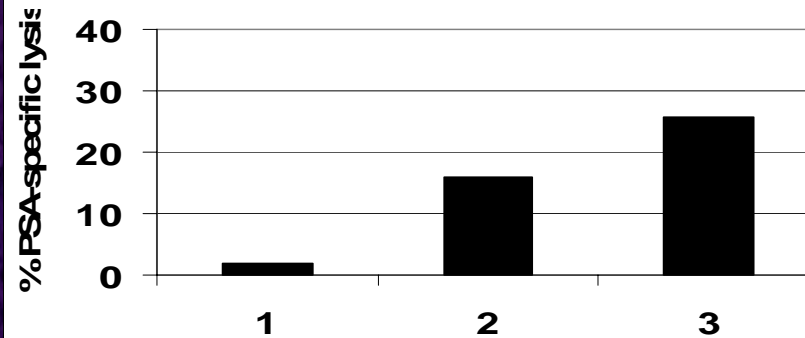


pPSA/pIL-18

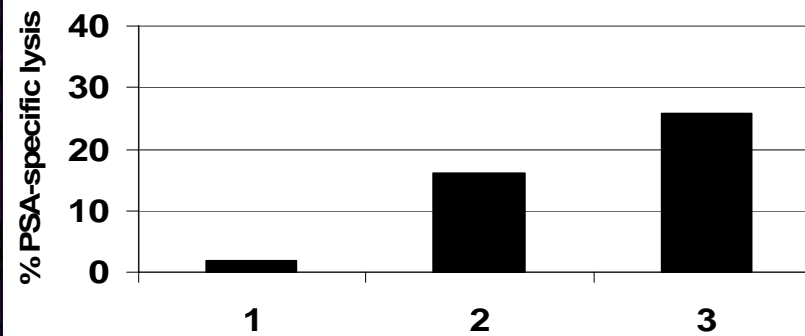


Green – P815/PSA  
Red – P815/EV

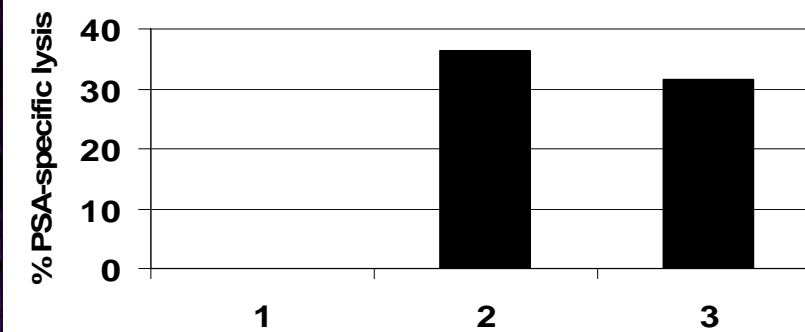
# pIL-18 Immunization enhances early CTL responses



**1 inoculation**



**2 inoculations**



**3 inoculations**

1 – Empty Vector  
2- pPSA  
3- pPSA + pIL-18



# Conclusions

- ◆ pPSA DNA vaccine induces protection against PSA-expressing tumors in a Balb/c syngeneic model
- ◆ Suboptimal doses of pPSA are protective when pIL-18 is coadministered
- ◆ Both CD4<sup>+</sup> and CD8<sup>+</sup> T cells played an important role in in vivo tumor protection
- ◆ pPSA DNA vaccine elicited strong Th1 immune responses in Balb/c mice with increased CD4<sup>+</sup> and CD8<sup>+</sup> effector T cell frequencies.
- ◆ pIL-18 enhanced the kinetics and intensity of the antigen-specific Th1 immune response elicited by pPSA
- ◆ IL-18 is a powerful adjuvant that enhances immune response induction and vaccine efficacy



# Acknowledgments

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